CLAIMS

Sub A1

1. A method of providing a mixture of DNA fragments enriched in fragments that are characteristic of a phenotype of interest, by providing affected DNA in fragmented form and providing unaffected DNA in fragmented form, which method comprises:

a) mixing the fragments of the affected DNA and the fragments of the unaffected DNA under hybridising conditions;

b) recovering a mixture of hybrids that contain mismatches;

c) recovering fragments of the affected DNA from the mixture of hybrids that contain mismatches;

and optionally repeating steps a), b) and c) one or more times.

Sub A1

2. The method of claim 1 wherein the affected DNA is pooled DNA of individuals who show the phenotype of interest, and the unaffected DNA is pooled DNA of individuals who do not show the phenotype of interest.

3. The method of claim 1, wherein the affected DNA is DNA of one individual who shows the phenotype of interest, and the unaffected DNA is pooled DNA of individuals who do not show the phenotype of interest.

4. The method of claim 1, wherein the affected DNA is DNA of one individual who shows the phenotype of interest, and the unaffected DNA is pooled DNA of a complete set of ancestors who do not show the phenotype of interest.

5. The method of claim 1, wherein the affected DNA is DNA from cells of an individual that show the phenotype of interest, and the unaffected DNA is DNA from cells of the individual that do not show the phenotype of interest.

6. The method of any one of claims 1 to 5, wherein step b) is performed by use of a mismatch-binding protein.

7. The method of any one of claims 1 to 6, wherein either the fragments of the affected DNA or the fragments of the unaffected DNA are tagged by one member of a specific binding pair, and step c) is performed by using the other member of the specific binding pair.

8. The method of claim 7, wherein the fragments of the unaffected DNA are tagged with biotin, and step c) is performed by use of immobilised streptavidin.

9. The method of any one of claims 1 to 8, wherein the mixture of DNA fragments enriched in fragments that are characteristic of the phenotype of interest, is subjected to self-hybridisation followed by recovery of perfectly matched duplexes.

10. The method of any one of claims 1 to 9, wherein the mixture of DNA fragments enriched in fragments that are characteristic of the phenotype of interest, is mixed with an excess of the fragments of the affected DNA under hybridisation conditions, followed by recovery of perfectly matched duplexes.

Sub A2

Sub A3

Sub A3

11. The method of any one of claims 1 to 10, wherein each of the affected DNA and the unaffected DNA is provided in fragmented form by digestion with from 4 to 7 six-cutter restriction endonuclease enzymes together with from 0 to 5 four-cutter restriction endonuclease enzymes.

12. A mixture of DNA fragments enriched in fragments that are characteristic of the phenotype of interest, provided by the method of any one of claims 1 to 11.

13. A method of making a set of arrays of fragments of DNA of interest, which method comprises:

a) selecting, from a set of n restriction endonuclease enzymes, a subset of r restriction endonuclease enzymes;

b) digesting genomic DNA with the subset of r enzymes;

c) ligating to the resulting fragments restriction-enzyme-cutting-site-specific adapters with unique polymerase chain reaction amplifiable sequences;

d) splitting the resulting fragments into r^2 aliquots;

e) amplifying each aliquot with two restriction-enzyme-specific primers of which one is tagged;

f) forming an array of the r^2 aliquots of non-tagged amplimer strands; and

g) repeating steps a) to f) using one or more different subsets of r restriction endonuclease enzymes.

14. A method of making a set of arrays of fragments of DNA of interest, which method comprises:

a) selecting, from a set of n restriction endonuclease enzymes, a subset of r restriction endonuclease enzymes;

b) digesting genomic DNA with the subset of r enzymes;

c) ligating to the resulting fragments restriction-enzyme-cutting-site-specific adapters with unique polymerase chain reaction amplifiable sequences;

d) splitting the resulting fragments into r^2 aliquots;

e) amplifying each aliquot with two restriction-enzyme-specific primers;

f) forming an array of the r^2 aliquots of the amplimer strands; and

g) repeating steps a) to f) using one or more different subsets of r restriction endonuclease enzymes.

15. The method of claim 13 or claim 14, wherein steps a to f) are repeated using each different subset of r restriction endonuclease enzymes to give (n!)/[(n-r)!r!] different arrays.

16. The method of any one of claims 13 to 15, wherein the n restriction endonuclease enzymes are selected from 4-cutters and 5-cutters and 6-cutters.

17. The method of any one of claims 13 to 16, wherein n is 3 to 10 and r is 2 to 4.

18. The method of claim 17, where n = 6 and r = 3.

19. A set of arrays of fragments of DNA of interest, which set results from performance of the method of any one of claims 13 to 18.

20. The set of arrays of claim 19, which set results from performance of the method of claim 13 and claim 14 and claim 15.

21. The set of arrays of claim 19 or claim 20, derived from a set of n = 6 six-cutter restriction endonuclease enzymes which are *BamHI; Bsr GI; Hind III; NcoI; SpeI;* and *AflII.*

22. The set of arrays of claim 19 or claim 20, derived from the set of n = 6 six-cutter restriction endonuclease enzymes which are *EcoRI; BspHI; BglII; XbaI; Acc65I;* and *ApaLI.*

23. A nucleic acid characterisation method which comprises presenting to the set of arrays of any one of claims 19 to 22 a nucleic acid fragment of interest under hybridisation conditions, and observing a pattern of hybridisation.

24. The method of claim 23, wherein a plurality of nucleic acid fragments of interest are separately presented to the set of arrays, and the resulting patterns of hybridisation are compared.

25. The method of claim 24, wherein the plurality of nucleic acid fragments of interest are drawn from the mixture of DNA fragments, enriched in fragments that are characteristic of a phenotype of interest, of claim 13.

26. A method of identifying fragments of DNA that are characteristic of a phenotype of interest, which method comprises recovering, cloning and amplifying individual DNA fragments from the mixture of DNA fragments of claim 12, presenting the individual DNA fragments to the set of arrays of any one of claims 19 to 22 under

hybridisation conditions, observing a pattern of hybridisation generated by each individual DNA fragment, and subjecting to further investigation any two or more individual DNA fragments whose hybridisation patterns are similar or identical, or near to each other in a genome of interest.

27. A double-stranded DNA molecule having the sequence a-A-b-B...X-y-Y-z where A, B...X and Y are unique restriction sites for n different restriction endonuclease enzymes, and a, b...y, z denotes distances in base pairs, characterised in that each fragment, obtainable by cutting the DNA molecule by means of any one or more up to n of the restriction enzymes, has a different length from every other fragment.

28. The double-stranded DNA molecule of claim 27, wherein the following criteria are satisfied:

a) inter-fragment length differences are greater for larger fragments;

b) all possible fragments are unambiguousiy resolvable by electrophoresis from one another;

c) size gaps between bands comprising different numbers of inter-restriction-site units are larger than size gaps between bands comprising the same number of inter-restriction-site units;

d) the size gaps and size spread from the largest to the smallest fragment are electrophorectically compatible.